AD-A157 120 EFFECT OF DERMAL APPLICATIONS OF PARANITROPHENOL ON THE REPRODUCTIVE FUNCTIONS OF RATS(U) ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GROUND MD 1/1

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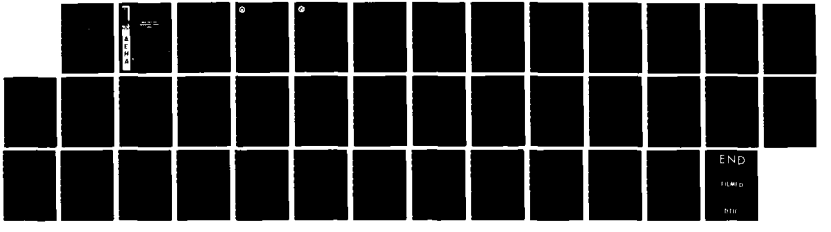
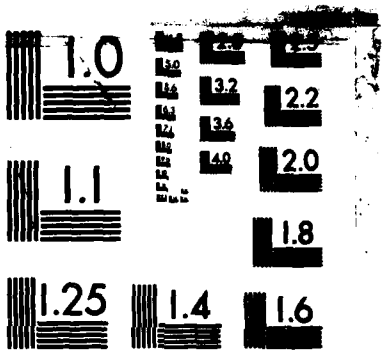
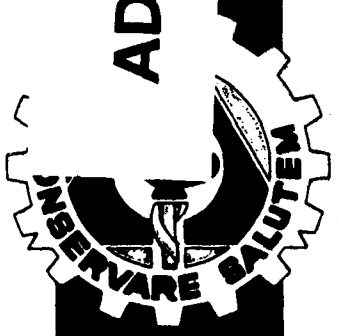


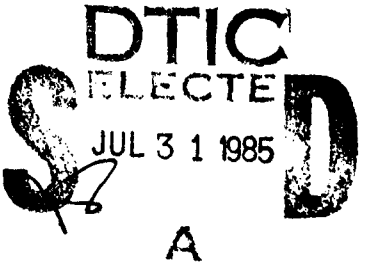




UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010-5422

FINAL PHASE
EFFECT OF DERMAL APPLICATIONS OF PARANITROPHENOL
ON THE REPRODUCTIVE FUNCTIONS OF RATS
STUDY NO. 75-51-0047-85
SEPTEMBER 1980 - MARCH 1985



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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The reproductive hazards of paranitrophenol, a leather fungicide, was assessed in rats. Compound, at various dosage levels, was administered dermally to parental and subsequent two generations. No significant differences in mating, pregnancy, behavior or growth were found when PNP-treated groups were compared with control groups. All rats receiving PNP, dermally, experienced a dose-related pattern of skin irritation. Paranitrophenol was found not to be a reproductive hazard in rats.

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

Mr. Angerhofer/orl/AUTOVON
584-3627

REPLY TO
ATTENTION OF

HSHB-OT

17 JUL 1985

SUBJECT: Final Phase, Effect of Dermal Applications of Paranitrophenol on the Reproductive Functions of Rats, Study No. 75-51-0047-85, September 1980 - March 1985

HQDA(DASG-PSP)
WASH DC 20310-2300

EXECUTIVE SUMMARY

The purpose, essential findings and conclusions of the enclosed report follow:

a. Purpose. US Army Natick Research and Development Center is attempting to permanently register paranitrophenol (PNP) as a leather fungicide with the Environmental Protection Agency. Information on the reproductive effects of PNP in rats was obtained to support this registration in accordance with the Federal Insecticide, Fungicide and Rodenticide Act. This study was conducted to determine the effects, if any, of dermal applications of PNP on parental rat activities from mating through lactation and in growth and development of offspring from conception through maturity.

b. Essential Findings. No significant differences in mating, pregnancy, behavior and growth were found in parents or subsequent two generations when PNP-treated groups were compared with a control group. All rats receiving PNP, dermally, experienced a dose-related pattern of skin irritation consisting of erythema, scaling, and cracking.

c. Conclusions. Under the conditions of this study, PNP was found not to be a reproductive hazard in rats. Although safe for its intended use, concentrated solutions of that compound should be handled using appropriate personal protection.

FOR THE COMMANDER:

Encl

JOBLVC. GAYDOS
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Director, Occupational and
Environmental Health

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO
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FINAL PHASE
EFFECT OF DERMAL APPLICATIONS OF PARANITROPHENOL ON THE REPRODUCTIVE FUNCTIONS OF RATS
STUDY NO. 75-51-0047-85
SEPTEMBER 1980 - MARCH 1985

1. AUTHORITY. Letter, US Army Natick Research and Development Command, DRXNM-ZT, 31 August 1977, subject: Toxicological Studies Required for Registration of Paranitrophenol as a Leather Fungicide, and endorsements thereto.

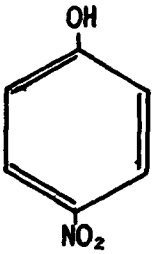
2. REFERENCES. See Appendix A for a list of references.

3. PURPOSE. This study was conducted to determine the effects, if any, of dermal applications of paranitrophenol (PNP) on parental rat activities from mating through lactation and in growth and development of offspring from conception through maturity. This investigation forms a part of the requirements for obtaining registration of PNP with the US Environmental Protection Agency (EPA) as a leather fungicide (EPA File No. 40510-E) (Appendix A, reference 1). The dermal route is the expected mode of human exposure.

4. BACKGROUND. The US Army has incorporated PNP into leather combat boots for fungicidal purposes for at least 30 years. Recent developments have mandated a requirement by the EPA to register the compound for that particular use. Since PNP is considered to be a "pesticide," guidelines were adopted in order to secure registration (Appendix A, reference 2). Appendix A, reference 3, set forth a protocol for a multigeneration reproduction study which was then modified by this Agency to accommodate a 5-day workweek and dermal application of the compound (Appendix A, references 4 and 5).

5. MATERIALS.

a. Paranitrophenol, CAS number 100-02-7, is a buff-colored, flaked solid with a musty odor. It is also identified as 4-Hydroxynitrobenzene and 4-Nitrophenol. Paranitrophenol is soluble in alcohol, ether and hot water. The molecular weight is 139.12; its imperical formula is $NO_2C_6H_5$, and its structure is shown below:



The material used in this study was supplied by E. I. DuPont de Nemours and Co., Inc., Organic Department, Dyes and Chemicals Division, Wilmington, Delaware 19898, and was contained in a heavy cardboard drum. The label carried a warning statement and the name, Paranitrophenol Tech. It was indicated on the container that the compound purity was 99.10 percent, Lot 1247E.

b. Absolute (100 percent) ethanol was the vehicle used to dissolve PNP to a concentration of 500 mg/mL.

c. Normal saline used for this study was identified as 0.9 percent NDC 0074-1583-05, Abbott Laboratories, Lot No. 15-328-DM-OG, expiring April 1984.

6. ANIMALS AND DOSAGE SELECTION.

a. One hundred twenty-six female and sixty-three male Sprague-Dawley rats were purchased from Charles River Breeding Laboratories, Kingston, New York. Rats were coded Crl: COBS-CD-(SD) BR colony animals and delivered at 4 weeks of age. For 2 days after arrival, like-sexed rats were housed three rats per cage in suspended wire cages, 21 cm wide, 31 cm deep and 21 cm high. Using a table of random numbers, the animals were then removed, consecutively numbered using a system of toe clip and ear punch and returned to their respective cages.

b. Again using a table of random numbers, six female and three male rats were selected for complete necropsy for quality assurance, including microbiology and histopathology to evaluate for any parameters which might adversely effect the study. Seven days after arrival, the animals, were released by the veterinarian in charge for study start.

c. At the onset of the study, the female rats were housed in the previously-mentioned cages, two females per unit. Males were placed in like cages, but housed individually. Food and water were provided ad libitum. Throughout the study, animal rooms were maintained at temperatures of 68-72° F with a relative humidity of between 40 and 60 percent. Fluorescent lighting was provided between the hours of 0600 and 1800 daily.

d. Three dosage levels of PNP, an ethanol (ETOH) control and a saline control were employed. On the day of study start, rats were randomly assigned to any one of the five groups. Each group consisted of 24 females and 12 males.

e. All rats were clipped free of hair, using electric clippers, along the dorsal body line over an area approximately 4 cm wide and 10 cm long. Throughout the dosing period, the rats were reshaved as necessary to allow good skin contact when the test materials were applied.

f. Dosing periods were lengthened over those proposed by EPA to compensate for this Agency's policy of a 5-day workweek. Test agents were applied dermally to both sexes, using appropriate-sized syringes, once daily, 5 days a week for the specified dosing period. Animals were individually weighed at the beginning of each week, at which time the dose values were adjusted for that week based on current body weight.

g. Paranitrophenol was dissolved in 100 percent ethanol to a concentration of 500 mg/mL. This solution, made up approximately every 3 days, was used for all three PNP dosage groups. The groups in this study are listed as follows:

Group I: Ethanol Control: 0.5 mL ETOH/kg/day

Group II: Saline Control: 0.5 mL Physiological Saline/kg/day

Group III: PNP Low: 50 mg PNP/kg/day

Group IV: PNP Mid: 100 mg PNP/kg/day

Group V: PNP High: 250 mg PNP/kg/day

Dosages of PNP are based upon a range-finding study which showed that a dosage of that compound which equated to one fourth of the dermal LD_{50} in rats (250 mg/kg) should not prove lethal to more than 10 percent of animals receiving that amount on a daily basis.

7. METHODS.

a. The original 120 female and 60 male rats were designated as the F_0 generation. These were dosed dermally 5 days a week for the first 140 days of the study (100 applications each). Following this period, half of the females in each group were paired with corresponding males until either positive mating was achieved, or it became evident that the pair would not mate (positive mating was determined by the presence of sperm plugs and verified by vaginal smear). When positive mating was achieved, the females were removed and housed individually in polycarbonate cages containing bedding material. The process was continued until it became apparent that no further mating would be accomplished within the timeframe allotted for the mating procedure.

b. The F_0 males were then held in individual cages for several days while dosing continued. After this time, they were sacrificed by decapitation, and testes, epididymis and skin sections were taken for histopathologic examination.

c. Dosing of the F_0 females continued through the breeding, gestation and lactation periods. Female doses during gestation were based upon the last premating weight.

d. Approximately 21 days after birth, the F_1 generation was weaned into wire cages, taking care to keep weanlings from different litters and test groups separated. The F_0 females were sacrificed by decapitation, and ovaries, uterus and skin sections were taken for histopathologic examination.

e. Using a table of random numbers, five F_1 weanlings of each sex from each test group were selected for complete necropsy with tissues taken for histopathology (a total of 50 weanlings). Additionally, any grossly abnormal F_1 weanlings were removed and submitted for complete necropsy.

f. On the weaning date, the selection of F_1 males and females to be used in the continuation of the study was made. The random table was used to select one-third of the litters from each test group from which 13 male rats were selected for dosing and breeding the F_2 generation. From the remaining two-thirds of the F_1 litters, 26 females were randomly selected for dosing and breeding the F_2 generation. This procedure prevented severe inbreeding while allowing random selection of breeding pairs.

g. The selected F_1 rats were numbered, housed, shaved and dosed in the same manner as the F_0 rats. Application of test materials continued over the next 168 days (120 applications each). Following this period, the F_1 rats were mated in a procedure corresponding to the mating of the F_0 parental animals.

h. Using a table of random numbers, five F_2 males and five F_2 females were selected from each group for complete necropsy at the time of weaning. An additional five F_2 males and five F_2 females from each group were randomly selected and retained in wire cages for 30 days after weaning. Dosing of all F_1 rats continued throughout breeding, gestation, lactation and until 30 days after all F_2 rats had been weaned. At this time, all F_1 rats and remaining F_2 rats (F_2 "holds") were submitted for complete necropsy.

i. In addition to the periodic sacrifices mentioned above, any animal dying spontaneously during the course of the study was submitted for necropsy. All rats submitted for necropsy were subjected to gross examination of external surfaces; orifices; brain and spinal cord; thoracic, abdominal and pelvic cavities and organs therein. Where complete necropsies were indicated, sections of the following organs were taken for histopathology: brain, spinal cord, eye, salivary gland, heart, thymus, thyroid, lungs, bronchi, esophagus, stomach, small intestine, large intestine, pancreas, adrenal glands, kidneys, liver, testes, epididymis, urinary bladder, male accessary glands, ovaries, corpus uteri, cervix uteri, spleen, lymph node, sternum, femur, skeletal muscle, mammary gland, treated skin and untreated skin. Organ weights were recorded for liver, kidneys, heart, gonad, and brain.

j. Observations for toxic signs, breeding and nesting behavior were recorded daily. Weights of all dosed rats were recorded weekly. The breeding and litter observations included general condition and behavior of the dams; litter size; individual pup weights and viability at birth, days 4, 7, 14 and at weaning. The following indices were calculated to assess reproductive success: fertility (number of pregnancies/number mated); gestation (percentage of pregnancies resulting in birth of live litters); viability (pups surviving at least to day 4 of life) and lactation (pups surviving at least to day 21 of life).

8. RESULTS.

a. F_0 Generation.

(1) Toxic Signs. All rats receiving PNP experienced a dose-related pattern of dermal irritation consisting of varying degrees of erythema, scaling, scabbing and cracking. After 15 weeks of dosing, several rats, especially males, showed transient hyperexcitability (i.e. jumping when handled). No other compound-linked gross signs were observed with the exception of the spontaneous death of a male rat, PNP, 250 mg/kg/day after 17 weeks of dosing and another male rat, PNP, 50 mg/kg/day after 24 weeks of dosing.

(2) Body Weight. All F_0 dosage groups, male and female, produced normal growth patterns throughout their test period. No significant differences in mean group body weight was detected when PNP dosage groups were compared with saline controls. A summary of F_0 body weight data is presented in Appendices B and C.

(3) Mating and Pregnancy. Positive mating was observed in as few as 15/24 in the group receiving PNP, 50 mg/kg/day, and in as many as 23/24 for the group receiving PNP, 250 mg/kg/day. The fertility index (pregnancy/mating) ranged from 58 percent for PNP, 100 mg/kg/day, to 87 percent in groups receiving PNP, 50 and 250 mg/kg/day. Fertility indices for controls fell within those extremes. All pregnancies resulted in the birth of viable litters (Appendix P).

(4) Necropsy Findings. Compound-related lesions were found only in the skin. Chronic inflammation, acanthosis, sebaceous hypertrophy, eschar formation, ulceration and ballooning degeneration of the stratum spinosum were observed in all dosage groups. The lowest incidence of these findings was in the saline controls while the group receiving PNP, 250 mg/kg/day, exhibited the highest incidence. F_0 testes-to-body weight ratios were not affected by PNP administration (Appendix F).

b. F_1 Generation.

(1) F_1 Viability and Toxic Signs. Survivability from birth to weaning was at or near 100 percent for pups in all dosage groups (Appendix P). Upon commencement of dosing of the F_1 generation, dermal irritation was

noted as in the F_0 generation. One male saline control died spontaneously during the 27th week of F_1 treatment. Two females, one ethanol control and one mid-level PNP, were sacrificed as moribund the following week. No compound-related lesions were found in these animals.

(2) Body Weight. All F_1 dosage groups, male and female, produced normal growth patterns throughout life. Male rats in the PNP, 250 mg/kg/day, group were consistently heavier than saline control males starting at the 9th week of dosing and continuing until sacrifice. No such trend existed for the other PNP-treated males. A summary of F_1 body weight data is presented in Appendices D and E.

(3) Mating and Pregnancy. Positive mating of F_1 females occurred in 21 ethanol controls; 22 saline controls; 17 PNP, 50 mg/kg/day; 18 PNP, 100 mg/kg/day; and 24 PNP, 250 mg/kg/day. The fertility index ranged from 50 percent for saline controls to 88 percent for females receiving PNP, 50 mg/kg. All pregnancies resulted in the birth of viable litters (Appendix Q).

(4) Necropsy Findings. Compound-related lesions were found only in the skin and approximated those in the F_0 generation. No consistent organ to body weight ratio changes were found at time of necropsy in liver, kidneys, heart, brain or gonads (Appendices G-K). No neoplasms were found which could be considered to be associated with administration of test compound.

c. F_2 Generation.

(1) Survival. Ninety-six to 100 percent of F_2 pups survived from birth to weaning in all dosage groups (Appendix Q). Those pups held for 30 days post weaning were normal in appearance, behavior and growth.

(2) Necropsy Findings. No significant pathological lesions were found in the F_2 generation with the exception of one true hermaphrodite among the PNP, 100 mg/kg/day, F_2 weanlings. Organ-to-body weight ratios of F_2 rats showed no dose-related shifts (Appendices L-O).

d. Quality Assurance. The quality assurance performed for this study is summarized in Appendix R.

9. CONCLUSIONS.

a. Paranitrophenol, administered dermally to two successive generations of parental rats, had no adverse effect on reproductive performance.

b. Offspring of PNP-dosed parents were unaffected by that compound in appearance, behavior and growth.

c. Relatively poor mating performance in all control and test groups appears to have been a function of age. The rats in this study (F_0 and F_1) were under treatment over a longer timespan then usually recommended in standard test protocols.

d. All groups treated with PNP displayed a dose-related skin irritation response after only a few applications and continuing throughout treatment. Histopathologic findings indicate that the ethanol used for the vehicle might have been a contributing factor in irritant effects.

10. RECOMMENDATIONS. The following recommendations are based on 43 FR 37384-37388 and 43 FR 44089-44092.

a. Use this reproduction study as a part of the basis for continued EPA registration of PNP as a fungicide to be used in military footwear.

b. Complete chronic animal toxicity studies in order to assure continued registration.

Richard A. Angerhofer

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Biologist
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APPROVED:

Maurice H. Weeks

MAURICE H. WEEKS
Chief, Toxicology Division

APPENDIX A

REFERENCES

1. Letter, US Army Environmental Hygiene Agency (USAEHA), HSE-LT, 21 August 1979, subject: Transmittal of Test Data: Paranitrophenol (Agency Special Study No. 75-51-0047-79), Phase 1.

2. Proposed Guidelines for Registering Pesticides in the United States; Hazard Evaluation: Humans and Domestic Animals, 43 Federal Register (FR) 37384-37388, 22 August 1978.

3. Proposed Rules, Health Effects Test Standards for Toxic Substances Control Act Test Rules and Proposed Good Laboratory Practice Standards for Health Effects, 44 FR 44089-44092, 26 July 1979.

4. Handbook of Teratology, Vol IV, Chapter 7, "Multigeneration Reproduction Studies," by T. F. X. Collins, p. 191-214, 1978.

5. USAEHA, Toxicology Division Standing Operating Procedures, Revised 1980-1981.

SUMMARY OF F_0 MALE BODY WEIGHTS (gms)

Group		Pre-Application	3 Doses	8 Doses	13 Doses	18 Doses	23 Doses	28 Doses	35 Doses	38 Doses	43 Doses	48 Doses
Saline Control	x	114	165	219	252	296	328	350	371	379	396	417
	±SD	8	13	16	20	25	28	34	34	36	37	35
Ethanol Control	x	114	167	220	258	303	345	362	386	401	415	434
	±SD	8	14	20	24	33	29	39	40	43	47	49
	t	0.04	0.31	0.11	0.72	0.58	1.52	0.84	1.00	1.34	1.11	0.96
	DF	22	22	22	22	22	22	22	22	22	22	22
PNP 50 mg/kg	x	107	161	213	252	294	328	354	378	385	403	418
	±SD	12	17	20	20	20	21	26	30	31	33	35
	t	1.53	0.65	0.80	0.02	0.25	0.01	0.36	0.55	0.48	0.46	0.12
	DF	22	22	22	22	22	22	22	22	22	22	22
PNP 100 mg/kg	x	112	160	212	247	292	326	345	368	377	398	415
	±SD	8	11	14	19	25	29	41	35	39	39	39
	t	0.49	1.15	1.15	0.52	0.45	0.16	0.27	0.17	0.11	0.08	0.09
	DF	22	22	22	22	22	22	22	22	22	22	22
PNP 250 mg/kg	x	108	163	215	252	292	324	348	369	379	396	413
	±SD	9	13	20	24	27	30	33	37	39	39	43
	t	1.70	0.43	0.60	0.07	0.35	0.29	0.14	0.18	0.06	0.01	0.21
	DF	22	22	22	22	22	22	22	22	22	22	22

APPENDIX F

SUMMARY OF F_0 MALE TESTES/BODY WEIGHT RATIOS

Group		Mean Terminal Weight	Mean Testes Weight Grams/100 Gram Weight Testes
Saline Control	x	494	0.71
	±SD	53	0.12
Ethanol Control	x	517	0.72
	±SD	61	0.08
	t	0.96	0.05
	DF	22	21
PNP 50 mg/kg	x	500	0.69
	±SD	59	0.12
	t	0.23	0.57
	DF	22	21
PNP 100 mg/kg	x	496	0.73
	±SD	45	0.08
	t	0.10	0.30
	DF	22	22
PNP 250 mg/kg	x	484	0.68
	±SD	60	0.14
	t	0.44	0.67
	DF	22	21

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SUMMARY OF F_1 FEMALE BODY WEIGHTS (gms)

Group		165 Doses	170 Doses	175 Doses	180 Doses
Saline Control	x	320	314	315	320
	±SD	32	29	30	31
Ethanol Control	x	318	311	308	307
	±SD	41	40	42	41
	t	0.20	0.28	0.80	1.34
	DF	49	49	49	49
PNP 50 mg/kg	x	319	313	311	313
	±SD	34	36	35	35
	t	0.20	0.07	0.53	0.80
	DF	50	50	50	50
PNP 100 mg/kg	x	311	309	306	306
	±SD	37	34	29	27
	t	0.93	0.61	1.25	1.76
	DF	49	49	49	49
PNP 250 mg/kg	x	320	305	313	317
	±SD	37	41	43	48
	t	0.06	0.60	0.33	0.35
	DF	50	50	50	50

SUMMARY OF F_1 FEMALE BODY WEIGHTS (gms)

Group		110 Doses	115 Doses	120 Doses	125 Doses	130 Doses	135 Doses	140 Doses	145 Doses	150 Doses	155 Doses	160 Doses
Saline Control	x	290	292	291	296	297	300	308	318	309	319	326
	±SD	29	29	30	31	30	31	34	41	32	32	33
Ethanol Control	x	274	277	275	281	281	287	298	321	311	322	326
	±SD	31	32	35	33	35	39	46	45	28	46	44
	t	1.97	1.73	1.82	1.76	1.77	1.44	0.91	0.22	0.21	0.28	0.10
	DF	50	50	50	50	50	50	50	49	49	49	49
PNP 50 mg/kg	x	278	280	279	283	285	289	298	310	507	319	319
	±SD	27	28	28	28	30	29	32	42	32	40	3
	t	1.63	1.49	1.52	1.59	1.43	1.39	1.05	0.67	0.30	0.07	0.69
	DF	50	50	50	50	50	50	50	50	50	50	50
PNP 100 mg/kg	x	276	278	277	281	285	289	294	307	314	325	314
	±SD	26	25	27	28	30	28	35	35	42	50	33
	t	1.83	1.84	1.78	1.82	1.49	1.38	1.45	0.97	0.44	0.53	1.22
	DF	50	50	50	50	50	50	50	49	49	49	49
PNP 250 mg/kg	x	284	287	285	286	288	294	307	320	329	311	323
	±SD	38	38	38	35	42	38	35	34	48	35	33
	t	0.66	0.59	0.65	1.15	0.96	0.71	0.07	0.19	1.71	0.79	0.23
	DF	50	50	50	50	50	50	50	50	50	50	50

SUMMARY OF F_1 FEMALE BODY WEIGHTS (gms)

Group		55 Doses	60 Doses	65 Doses	70 Doses	75 Doses	80 Doses	85 Doses	90 Doses	95 Doses	Mating Began 100 Doses	105 Doses
Saline Control	x	241	249	253	261	266	261	272	272	274	279	284
	±SD	22	23	24	25	24	25	25	25	26	25	26
Ethanol Control	x	229*	237	241	253	257	253	260	265	264	269	274
	±SD	22	27	25	26	27	26	26	27	29	31	30
	t	2.05	1.68	1.67	1.07	1.35	1.07	1.67	0.85	1.37	1.34	1.33
	DF	50	50	50	50	50	50	50	50	50	50	50
PNP 50 mg/kg	x	236	242	245	256	260	256	263	268	265	272	274
	±SD	28	23	24	25	25	25	25	26	24	25	26
	t	0.99	1.11	1.21	0.70	0.96	0.70	1.28	0.45	1.32	1.28	1.34
	DF	50	50	50	50	50	50	50	50	50	50	50
PNP 100 mg/kg	x	231	239	243	254	258	254	264	263	263	268	272
	±SD	20	21	22	23	25	23	23	25	25	23	24
	t	1.74	1.63	1.57	1.04	1.21	1.34	1.18	1.59	1.59	1.61	1.68
	DF	50	50	50	50	50	50	50	50	50	50	50
PNP 250 mg/kg	x	236	243	246	257	262	257	266	271	263	274	280
	±SD	28	29	27	28	30	28	30	33	29	33	36
	t	0.78	0.89	0.99	0.49	0.59	0.49	0.78	0.07	1.45	0.62	0.47
	DF	59	50	50	50	50	50	50	50	50	50	50

*Significantly different at the 0.05 level of probability.

APPENDIX E

SUMMARY OF F_1 FEMALE BODY WEIGHTS (gms)

Group		Pre-Application	5 Doses	10 Doses	15 Doses	20 Doses	25 Doses	30 Doses	35 Doses	40 Doses	45 Doses	50 Doses
Saline Control	x	47	66	102	135	155	175	192	207	220	230	237
	±SD	13	15	18	17	17	18	17	18	19	20	21
Ethanol Control	x	60	70	93	126	149	170	183	201	213	221	227
	±SD	2	12	27	27	23	21	22	21	22	22	21
	t	1.59	0.89	1.37	1.50	1.19	0.90	1.51	1.25	1.11	1.58	1.75
	DF	8	41	50	50	50	50	50	50	50	50	50
PNP 50 mg/kg	x	47	73	95	128	148	171	187	203	214	223	229
	±SD	4	13	28	26	21	18	18	17	19	20	20
	t	0.00	1.59	1.08	1.16	1.28	0.69	0.97	0.94	1.14	1.28	1.39
	DF	11	40	50	50	50	50	50	50	50	50	50
PNP 100 mg/kg	x	46	66	82*	113*	140*	165	182	199	210	220	228
	±SD	5	18	30	27	21	20	20	17	17	17	18
	t	0.29	0.12	2.88	3.59	2.75	1.76	1.91	1.73	1.88	1.88	1.56
	DF	13	36	50	50	50	50	50	50	50	50	50
PNP 250 mg/kg	x	45	62	93	127	150	169	186	201	214	223	230
	±SD	3	15	21	23	23	23	25	25	25	25	26
	t	0.36	0.82	1.66	1.50	0.96	0.97	1.00	1.09	0.89	1.10	0.96
	DF	10	43	50	50	50	50	50	50	50	50	50

*Significantly different at the 0.05 level of probability.

Study No. 75-51-0047-85, Sep 80 - Mar 85

SUMMARY OF F_1 MALE BODY WEIGHTS (gms)

Group		165 Doses	170 Doses	175 Doses	180 Doses	185 Doses	190 Doses
Saline Control	x	532	535	542	544	543	547
	±SD	39	40	43	41	40	42
Ethanol Control	x	516	528	527	530	527	534
	±SD	43	44	47	47	45	45
	t	0.99	0.49	0.85	0.82	0.90	0.76
	DF	23	23	23	23	23	23
PNP 50 mg/kg	x	532	537	540	542	543	549
	±SD	46	47	49	52	51	52
	t	0.02	0.04	0.10	0.11	0.04	0.13
	DF	23	23	23	23	23	23
PNP 100 mg/kg	x	531	535	540	541	537	544
	±SD	69	76	73	76	72	73
	t	0.04	0.05	0.10	0.14	0.24	0.14
	DF	23	23	23	23	23	23
PNP 250 mg/kg	x	591*	594*	602*	605*	602*	610*
	±SD	58	57	61	63	61	65
	t	3.00	2.93	2.85	2.82	2.83	2.86
	DF	23	23	23	23	24	23

*Significantly different at the 0.05 level of probability.

SUMMARY OF F_1 MALE BODY WEIGHTS (gms)

Group		110 Doses	115 Doses	120 Doses	125 Doses	130 Doses	135 Doses	140 Doses	145 Doses	150 Doses	155 Doses	160 Doses
Saline Control	x	491	498	494	501	505	491	497	498	507	516	523
	±SD	34	37	37	36	38	36	39	40	39	40	38
Ethanol Control	x	481	488	486	493	499	485	489	492	498	500	507
	±SD	40	41	40	41	41	42	42	40	40	41	43
	t	0.65	0.65	0.53	0.41	0.41	0.41	0.55	0.43	0.56	0.10	1.02
	DF	24	24	24	24	24	24	23	23	23	23	23
PNP 50 mg/kg	x	496	500	498	501	505	499	503	506	513	521	526
	±SD	37	39	40	327	37	39	41	40	42	45	45
	t	0.38	0.17	0.24	0.11	0.01	0.54	0.36	0.49	0.38	0.28	0.14
	DF	24	24	24	24	24	24	23	23	23	23	23
PNP 100 mg/kg	x	495	501	501	505	511	498	499	504	512	519	532
	±SD	64	68	65	67	66	63	62	60	61	60	67
	t	0.25	0.14	0.31	0.21	0.30	0.32	0.10	0.27	0.23	0.13	0.44
	DF	24	24	24	24	24	24	23	23	23	23	23
PNP 250 mg/kg	x	543*	551*	551*	552*	560*	544*	555*	561*	569*	577*	581*
	±SD	53	53	54	52	53	52	54	53	55	56	55
	t	2.99	3.00	3.02	2.91	3.02	3.00	3.03	3.32	3.20	3.10	3.03
	DF	24	24	24	24	24	24	23	23	23	23	23

*Significantly different at the 0.05 level of probability.

SUMMARY OF F_1 MALE BODY WEIGHTS (gms)

Group		55 Doses	60 Doses	65 Doses	70 Doses	75 Doses	80 Doses	85 Doses	90 Doses	95 Doses	Mating Began 100 Doses	105 Doses
Saline Control	x	392	412	422	435	443	452	469	467	469	475	487
	±SD	26	27	28	29	27	29	26	28	31	32	33
Ethanol Control	x	395	412	419	430	441	449	454	460	457	468	478
	±SD	35	37	37	37	37	36	38	38	35	40	40
	t	0.23	0.01	0.28	0.38	0.15	0.25	0.48	0.48	0.79	0.49	0.64
	DF	24	24	24	24	24	24	24	24	24	24	24
PNP 50 mg/kg	x	389	406	418	431	445	450	459	468	470	481	490
	±SD	33	33	33	31	34	35	34	35	37	35	38
	t	0.25	0.49	0.33	0.32	0.10	0.11	0.07	0.10	0.08	0.44	0.21
	DF	24	24	24	24	24	24	24	24	24	24	24
PNP 100 mg/kg	x	410	429	439	450	462	465	469	475	476	484	489
	±SD	46	45	48	46	48	50	55	59	61	62	67
	t	1.22	1.13	1.06	1.01	1.23	0.81	0.58	0.48	0.39	0.43	0.09
	DF	24	24	24	24	24	24	24	24	24	24	24
PNP 250 mg/kg	x	431*	454*	465*	480*	490*	495*	506*	514*	517*	530*	537*
	±SD	42	44	44	45	46	46	49	49	51	51	50
	t	2.80	2.90	2.98	3.06	2.89	2.89	3.02	3.00	2.94	3.31	2.98
	DF	24	24	24	24	24	24	24	24	24	24	24

*Significantly different at the 0.05 level of probability.

APPENDIX D

SUMMARY OF F_1 MALE BODY WEIGHTS (gms)

Group		Pre-Application	5 Doses	10 Doses	15 Doses	20 Doses	25 Doses	30 Doses	35 Doses	40 Doses	45 Doses	50 Doses
Saline Control	x	49	78	118	161	206	253	289	323	348	365	380
	±SD	17	18	18	33	32	33	31	28	28	27	26
Ethanol Control	x	50	79	113	164	206	252	289	322	348	368	385
	±SD	11	20	41	50	50	54	51	45	41	38	35
	t	0.05	0.12	0.35	0.16	0.00	0.07	0.00	0.06	0.06	0.22	0.36
	DF	7	20	24	24	24	24	24	24	24	24	24
PNP 50 mg/kg	x	70	69	102	147	186	228	272	309	335	358	375
	±SD	6	30	41	44	48	44	40	37	40	35	35
	t	2.01	0.89	1.13	1.32	1.27	1.64	1.20	1.08	1.98	0.56	0.46
	DF	5	20	24	24	24	24	24	24	24	24	24
PNP 100 mg/kg	x	57	95*	116	159	202	250	289	328	358	380	397
	±SD	5	8	48	57	61	62	57	51	48	46	46
	t	0.87	2.54	0.16	0.43	0.23	0.16	0.04	0.26	0.70	0.99	1.14
	DF	6	18	24	24	24	24	24	24	24	24	24
PNP 250 mg/kg	x	61	78	121	174	213	263	307	346	371	397*	414*
	±SD	1	24	31	34	34	34	32	37	41	40	42
	t	1.16	0.05	0.24	0.52	0.56	0.70	1.51	1.79	1.70	2.36	2.41
	DF	5	21	24	24	24	24	24	24	24	24	24

*Significantly different at the 0.05 level of probability.

Study No. 75-51-0047-85, Sep 80 - Mar 85

SUMMARY OF F_0 FEMALE BODY WEIGHTS (gms)

Group		108 Doses	113 Doses	118 Doses
Saline Control	x	295	332	315
	±SD	70	34	40
Ethanol Control	x	309	333	321
	±SD	24	28	42
	t	0.73	0.12	0.35
	DF	46	46	46
PNP 50 mg/kg	x	306	328	325
	±SD	21	21	47
	t	0.60	0.36	0.60
	DF	46	46	46
PNP 100 mg/kg	x	308	331	315
	±SD	33	45	27
	t	0.65	0.03	0.02
	DF	46	46	46
PNP 250 mg/kg	x	308	332	323
	±SD	20	24	48
	t	0.92	0.02	0.57
	DF	46	46	46

SUMMARY OF F_0 FEMALE BODY WEIGHTS (gms)

Group		53 Doses	58 Doses	63 Doses	68 Doses	73 Doses	78 Doses	83 Doses	88 Doses	Mating Began 93 Doses	98 Doses	105 Doses
Saline Control	x	252	256	259	265	266	269	271	274	276	246	291
	±SD	24	23	23	23	24	25	28	27	30	27	25
Ethanol Control	x	258	264	267	279	273	277	281	286	295*	287	291
	±SD	17	19	20	22	22	23	23	23	28	24	25
	t	0.98	1.06	1.29	1.09	1.01	1.25	1.35	1.55	2.17	1.11	0.06
	DF	46	46	46	46	46	46	46	46	46	46	46
PMP 50 mg/kg	x	251	257	258	267	268	271	273	273	279	277	288
	±SD	19	21	22	21	22	22	23	22	24	22	15
	t	0.17	0.04	0.05	0.24	0.18	0.38	0.28	0.16	0.36	0.24	0.34
	DF	46	46	46	46	46	46	46	46	46	46	46
PMP 100 mg/kg	x	256	260	260	268	270	273	272	279	282	280	290
	±SD	20	22	21	21	22	23	26	24	22	22	24
	t	0.56	0.55	0.19	0.73	0.59	0.64	0.19	0.61	0.74	0.23	0.05
	DF	46	46	46	46	46	46	46	46	46	46	46
PMP 250 mg/kg	x	253	258	261	268	269	273	278	278	277	279	291
	±SD	16	18	20	20	19	19	19	19	21	21	20
	t	0.17	0.23	0.28	0.86	0.24	0.61	1.01	0.50	0.08	0.06	0.02
	DF	46	46	46	46	46	46	46	46	46	46	46

*Significantly different at the 0.05 level of probability.

APPENDIX C

SUMMARY OF F_0 FEMALE BODY WEIGHTS (gms)

Group		Pre-Application	3 Doses	8 Doses	13 Doses	18 Doses	23 Doses	28 Doses	35 Doses	38 Doses	43 Doses	48 Doses
Saline Control	x	99	135	164	178	198	212	218	225	233	240	248
	±SD	12	13	13	14	14	16	20	24	20	21	21
Ethanol Control	x	102	135	165	181	200	216	226	231	235	247	254
	±SD	9	11	13	12	12	15	15	16	15	17	18
	t	1.04	0.08	0.17	0.61	0.47	0.68	1.50	1.02	0.55	1.14	1.02
	DF	46	46	46	46	46	46	46	46	46	46	46
PNP 50 mg/kg	x	99	132	159	176	193	207	219	228	231	239	245
	±SD	8	9	11	12	13	15	15	16	17	18	19
	t	0.12	0.88	1.40	0.68	1.39	1.18	0.07	0.46	0.37	0.25	0.54
	DF	46	46	46	46	46	46	46	46	46	46	46
PNP 100 mg/kg	x	101	137	165	181	199	212	222	230	235	242	251
	±SD	11	10	13	14	16	18	18	17	18	19	19
	t	0.82	0.56	0.25	0.53	0.12	0.10	0.72	0.83	0.25	0.25	0.42
	DF	46	46	46	46	46	46	46	46	46	46	46
PNP 250 mg/kg	x	96	133	160	197	197	211	222	230	233	240	248
	±SD	9	10	10	12	12	13	14	15	14	16	17
	t	0.87	0.62	1.22	0.40	0.40	0.27	0.64	0.81	0.11	0.12	0.07
	DF	46	46	46	46	46	46	46	46	46	46	46

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SUMMARY OF F_0 MALE BODY WEIGHTS (gms)

Group		108 Doses	113 Doses
Saline Control	x	487	494
	±SD	49	51
Ethanol Control	x	517	517
	±SD	69	61
	t	1.19	1.00
	DF	22	22
PNP 50 mg/kg	x	496	506
	±SD	56	45
	t	0.40	0.52
	DF	22	22
PNP 100 mg/kg	x	492	496
	±SD	46	45
	t	0.21	0.01
	DF	22	22
PNP 250 mg/kg	x	484	490
	±SD	59	59
	t	0.15	0.15
	DF	22	22

SUMMARY OF MALE BODY WEIGHTS (gms)

Group		53 Doses	58 Doses	63 Doses	68 Doses	73 Doses	78 Doses	83 Doses	88 Doses	Mating Began 93 Doses	98 Doses	105 Doses
Saline Control	x	427	442	448	458	452	466	473	477	488	485	483
	±SD	36	39	38	42	42	41	42	45	45	45	47
Ethanol Control	x	447	459	466	475	484	491	500	509	516	514	507
	±SD	52	55	54	46	57	58	59	61	62	61	68
	t	1.05	0.86	0.93	0.93	1.54	1.18	1.29	1.43	1.22	1.30	1.04
	DF	22	22	22	22	22	22	22	22	22	22	22
PNP 50 mg/kg	x	483	445	449	464	467	471	482	483	493	478	488
	±SD	37	42	42	45	46	51	51	44	49	47	53
	t	0.35	0.20	0.04	0.32	0.83	0.29	0.44	0.31	0.21	0.39	0.27
	DF	22	22	22	22	22	22	22	22	22	22	22
PNP 100 mg/kg	x	429	440	448	462	461	470	478	483	491	491	489
	±SD	41	43	41	44	45	47	47	47	49	50	51
	t	0.08	0.07	0.01	00.24	0.49	0.20	0.24	0.31	0.13	0.29	0.32
	DF	22	22	22	22	22	22	22	22	22	22	22
PNP 250 mg/kg	x	425	437	445	459	455	464	475	475	473	475	477
	±SD	44	46	42	44	47	48	47	55	48	61	53
	t	0.17	0.26	0.20	0.03	0.13	0.14	0.07	0.09	0.81	0.43	0.25
	DF	22	22	22	22	22	22	22	22	22	22	22

APPENDIX G

SUMMARY OF F_1 MALE WEANLINGS ORGAN/BODY WEIGHT RATIOS

Group		Mean Terminal Weight	Mean Organ Weight Grams/100 Gram Weight				
			Liver	Kidney	Heart	Testes	Brain
Saline Control	x	54	4.7	1.2	0.5	0.6	2.7
	±SD	7	0.5	0.1	0.1	0.1	0.4
Ethanol Control	x	45	4.7	0.5	0.5	0.5	3.2
	±SD	11	0.9	0.0	0.1	0.1	0.4
	t	1.63	0.03	1.81	0.04	0.47	1.96
	DF	8	8	8	7	8	8
PNP 50 mg/kg	x	49	4	1.3	0.5	0.6	2.9
	±SD	6	0.9	0.1	0.0	0.1	0.4
	t	1.34	0.79	0.95	0.88	0.85	0.68
	DF	8	8	7	8	8	8
PNP 100 mg/kg	x	52	4.6	1.4	0.5	0.6	2.9
	±SD	13	0.3	0.1	0.0	0.2	0.5
	t	0.34	0.47	2.34	0.68	0.49	0.59
	DF	8	8	7	8	8	8
PNP 250 mg/kg	x	62	4.6	1.4	0.6	0.6	2.5
	±SD	14	0.6	0.1	0.1	0.0	0.5
	t	1.15	0.41	1.67	1.01	0.04	0.95
	DF	8	8	7	8	8	8

APPENDIX H

SUMMARY OF F_1 FEMALE WEANLINGS ORGAN/BODY WEIGHT RATIOS

Group		Mean Terminal Weight	Mean Organ Weight Grams/100 Gram Weight			
			Liver	Kidney	Heart	Brain
Saline Control	x	33	4.7	1.5	0.6	3.6
	±SD	8	0.7	0.3	0.1	0.7
Ethanol Control	x	52*	4.9	1.7	0.6	2.4
	±SD	10	0.6	0.8	0.1	1.0
	t	3.29	0.29	0.59	0.04	2.33
	DF	8	8	8	7	8
PNP 50 mg/kg	x	55*	4.3	1.3	0.5	2.7
	±SD	17	0.5	0.1	0.0	0.8
	t	2.59	1.08	1.16	0.45	1.90
	DF	8	8	8	8	8
PNP 100 mg/kg	x	38	4.2	1.4	0.6	3.4
	±SD	4	0.3	0.1	0.1	0.2
	t	1.27	1.35	0.51	0.17	0.47
	DF	8	8	8	8	8
PNP 250 mg/kg	x	45*	4.6	1.4	0.5	3.1
	±SD	8	0.4	0.1	0.0	0.3
	t	2.30	0.26	0.83	0.59	1.56
	DF	8	8	8	8	8

*Significantly different at the 0.05 level of probability.

APPENDIX I

SUMMARY OF F_1 MALE ORGAN/BODY WEIGHT RATIOS

Group		Mean Terminal Weight	Mean Organ Weight Grams/100 Gram Weight				
			Liver	Kidney	Heart	Testes	Brain
Saline Control	x	552	3.51	0.65	0.26	0.61	0.38
	±SD	44	0.28	0.03	0.02	0.15	0.03
Ethanol Control	x	53	3.61	0.64	0.28	0.65	0.40
	±SD	48	0.30	0.06	0.02	0.06	0.50
	t	0.75	0.89	0.43	2.30	0.95	0.87
	DF	23	23	23	23	23	23
PNP 50 mg/kg	x	553	3.24*	0.62	0.26	0.68	0.38
	±SD	53	0.35	0.05	0.02	0.12	0.05
	t	0.01	2.10	1.57	0.13	1.35	0.07
	DF	23	23	23	23	23	23
PNP 100 mg/kg	x	550	3.50	0.72*	0.27	0.63	0.40
	±SD	75	0.32	0.04	0.02	0.09	0.80
	t	0.11	0.09	4.66	1.50	0.39	0.82
	DF	23	23	23	23	23	23
PNP 250 mg/kg	x	613*	3.29	0.62	0.25	0.53	0.34*
	±SD	65	0.33	0.05	0.02	0.06	0.04
	t	2.71	1.71	1.91	1.51	1.92	2.82
	DF	23	23	23	23	23	23

*Significantly different at the 0.05 level of probability.

APPENDIX J

SUMMARY OF F, FEMALE (LITTER WEANED) ORGAN/BODY WEIGHT RATIOS

Group		Mean Terminal Weight	Mean Organ Weight Grams/100 Gram Weight				
			Liver	Kidney	Heart	Ovaries	Brain
Saline Control	x	308	3.84	0.79	0.35	0.05	0.64
	±SD	30	0.27	0.04	0.03	0.01	0.06
Ethanol Control	x	300	3.79	0.76	0.40	0.04	0.64
	±SD	28	0.30	0.06	0.09	0.01	0.06
	t	0.64	0.38	1.33	1.90	1.01	0.10
	DF	22	22	22	21	20	22
PNP 50 mg/kg	x	307	3.62	0.79	0.36	0.04	0.63
	±SD	27	0.29	0.04	0.04	0.01	0.06
	t	0.05	1.88	0.14	0.68	0.93	0.44
	DF	22	22	19	22	22	22
PNP 100 mg/kg	x	304	3.83	0.78	0.38	0.04	0.64
	±SD	25	0.30	0.08	0.10	0.01	0.04
	t	0.30	0.05	0.30	0.91	0.64	0.14
	DF	19	19	19	19	19	19
PNP 250 mg/kg	x	295	3.70	0.78	0.37	0.05	0.67
	±SD	48	0.23	0.08	0.03	0.01	0.11
	t	0.72	1.33	0.03	1.70	0.17	0.79
	DF	21	21	21	21	21	21

APPENDIX K

SUMMARY OF F_1 FEMALE (NOT PREGNANT) ORGAN/BODY WEIGHT RATIOS

Group		Mean Terminal Weight	Mean Organ Weight Grams/100 Gram Weight				
			Liver	Kidney	Heart	Ovaries	Brain
Saline Control	x	327	3.73	0.77	0.35	0.04	0.06
	±SD	31	0.34	0.06	0.03	0.02	0.06
Ethanol Control	x	321	3.71	0.76	0.34	0.05	0.62
	±SD	54	0.49	0.09	0.04	0.01	0.10
	t	0.41	0.11	0.52	0.24	0.49	0.59
	DF	25	25	25	25	25	25
PNP 50 mg/kg	x	318	3.72	0.75	0.36	0.04	0.62
	±SD	47	0.29	0.09	0.03	0.01	0.09
	t	0.64	0.04	0.06	0.74	0.25	0.71
	DF	26	26	26	26	26	26
PNP 100 mg/kg	x	311	3.64	0.81	0.36	0.04	0.62
	±SD	35	0.55	0.08	0.05	0.01	0.07
	t	1.33	0.51	1.35	1.00	1.30	0.92
	DF	28	28	28	28	28	28
PNP 250 mg/kg	x	337	3.66	0.75	0.33	0.03	0.57
	±SD	46	0.27	0.05	0.05	0.01	0.07
	t	0.67	0.55	1.00	1.39	1.96	1.09
	DF	27	27	27	27	27	27

APPENDIX L

SUMMARY OF F_2 MALE WEANLINGS ORGAN/BODY WEIGHT RATIOS

Group		Mean Terminal Weight	Mean Organ Weight Grams/100 Gram Weight				
			Liver	Kidney	Heart	Testes	Brain
Saline Control	x	66	4.5	0.6	0.5	0.6	2.5
	±SD	18	0.3	0.6	0.1	0.1	0.6
Ethanol Control	x	42*	3.9*	1.3	0.6	0.6	3.6
	±SD	14	0.4	0.1	0.1	0.1	1.3
	t	2.58	2.38	1.10	1.58	1.06	1.70
	DF	9	9	9	9	9	9
PNP 50 mg/kg	x	49	4.0	1.3	0.5	0.5	3.1
	±SD	10	0.7	0.1	0.1	0.1	0.5
	t	1.36	1.21	0.95	0.62	1.72	1.73
	DF	8	8	8	8	8	8
PNP 100 mg/kg	x	48	4.5	1.7	0.6	0.6	3.2
	±SD	13	0.5	0.8	0.1	0.1	0.9
	t	1.87	0.30	0.37	0.13	1.33	1.49
	DF	8	8	8	8	7	8
PNP 250 mg/kg	x	44	4.1	1.3	0.6	0.5*	3.5
	±SD	18	0.6	0.1	0.1	0.1	1.2
	t	0.40	1.34	1.05	0.85	3.46	1.79
	DF	8	10	9	10	10	10

*Significantly different at the 0.05 level of probability.

APPENDIX M

SUMMARY OF F_2 FEMALE WEANLINGS ORGAN/BODY WEIGHT RATIOS

Group		Mean Terminal Weight	Mean Organ Weight Grams/100 Gram Weight			
			Liver	Kidney	Heart	Brain
Saline Control	x	59	4.5	1.5	0.5	2.6
	±SD	10	0.2	0.2	0.1	0.4
Ethanol Control	x	46	4.5	1.3	0.6	2.7
	±SD	10	0	0.1	0.1	0.9
	t	2.00	0.22	1.54	0.42	0.13
	DF	9	9	9	7	9
PNP 50 mg/kg	x	49	4.1	1.4	0.6	3.2
	±SD	14	0.3	0.2	0.1	0.8
	t	1.39	1.96	0.42	0.22	1.57
	DF	9	9	9	9	9
PNP 100 mg/kg	x	42*	4.1	1.4	0.6	3.5*
	±SD	8	0.5	0.2	0.0	0.6
	t	3.24	1.67	0.70	0.67	2.77
	DF	10	10	10	10	10
PNP 250 mg/kg	x	45	4.0	1.5	0.6	3.1
	±SD	12	0.4	0.3	0.1	0.4
	t	1.92	2.05	0.24	0.04	1.67
	DF	8	8	8	8	8

*Significantly different at the 0.05 level of probability.

APPENDIX N

SUMMARY OF F_2 MALE HOLDS ORGAN/BODY WEIGHT RATIOS

Group		Mean Terminal Weight	Mean Organ Weight Grams/100 Gram Weight				
			Liver	Kidney	Heart	Testes	Brain
Saline Control	x	286	4.85	0.94	0.36	0.94	0.68
	±SD	51	0.39	0.09	0.03	0.09	0.11
Ethanol Control	x	269	5.02	0.92	0.37	0.94	0.68
	±SD	50	0.69	0.08	0.02	0.12	1.10
	t	0.52	0.49	0.44	0.63	0.06	0.06
	DF	8	8	8	8	8	8
PNP 50 mg/kg	x	283	4.62	0.86	0.35	0.98	0.64
	±SD	33	0.03	0.05	0.02	0.12	0.06
	t	0.10	1.30	1.69	0.59	0.62	0.61
	DF	8	8	8	8	8	8
PNP 100 mg/kg	x	263	4.95	0.96	0.38	0.95	0.68
	±SD	38	0.41	0.07	0.05	0.10	0.10
	t	0.85	0.42	0.38	0.64	0.20	0.09
	DF	9	8	8	8	8	8
PNP 250 mg/kg	x	251	4.87	0.89	0.38	0.85	0.71
	±SD	46	0.47	0.11	0.02	0.10	0.12
	t	1.13	1.10	0.89	0.96	1.54	0.52
	DF	8	8	8	8	8	8

APPENDIX O

SUMMARY OF F_2 FEMALE HOLDS ORGAN/BODY WEIGHT RATIOS

Group		Mean Terminal Weight	Mean Organ Weight Grams/100 Gram Weight				
			Liver	Kidney	Heart	Ovaries	Brain
Saline Control	x	187	4.68	1.10	0.42	0.07	0.94
	±SD	20	0.50	0.25	0.03	0.01	0.06
Ethanol Control	x	182	4.94	0.94	0.41	0.06	0.94
	±SD	17	0.32	0.07	0.03	0.01	0.06
	t	0.27	0.97	1.46	0.59	0.28	0.00
	DF	8	8	8	8	8	8
PNP 50 mg/kg	x	194	4.58	0.95	0.52	0.06	0.90
	±SD	11	0.15	0.04	0.21	0.01	0.07
	t	0.89	0.44	1.42	0.97	1.26	1.03
	DF	8	8	8	8	8	8
PNP 100 mg/kg	x	176	4.35	0.96	0.41	0.06	0.97
	±SD	21	0.42	0.11	0.05	0.01	0.10
	t	0.74	1.14	1.18	0.53	1.00	0.63
	DF	8	8	8	8	8	8
PNP 250 mg/kg	x	185	4.59	0.96	0.55	0.05	0.98
	±SD	21	0.55	0.10	0.30	0.01	0.05
	t	0.03	0.28	1.22	0.96	2.12	1.15
	DF	8	8	8	8	8	8

F_0 MATING AND F_1 SURVIVABILITY DATA

Group Number	I	II	III	IV	V
Dosage Group	Ethanol Control	Saline Control	PNP, 50 mg/kg	PNP, 100 mg/kg	PNP, 250 mg/kg
No. of Matings (F_0)	17	22	15	19	23
No. of Pregnancies	13	18	13	11	20
Fertility Index	76%	82%	87%	58%	87%
No. Litters Born	13	18	13	11	23
Gestation Index	100%	100%	100%	100%	100%
No. of Pups Born (F_1)	150	184	139	132	232
No. of Pups Born Alive	149	179	137	130	231
No. of Pups Alive Day 4	148	175	135	130	231
Viability Index	99%	97%	98%	98%	99%
No. of Pups Weaned	146	175	135	130	232
Lactation Index	99%	99%	100%	100%	100%
Mean Litter Size Born:	12.4	9.9	9.8	10.8	11.6
No. Male Pups	5.7	5.2	4.5	4.7	5.7
No. Female Pups	6.7	4.7	5.2	6.2	5.8
Mean Weight of Pups at 24 hrs:					
Males (g)	6.7	6.7	7.1	6.6	7.0
Females (g)	6.4	6.4	6.5	6.5	6.7
Mean Weight of Pups at Weaning:					
Males (g)	38.8	37.4	40.3	40.2	40.8
Females (g)	37.2	36.1	39.2	39.3	38.8

F_1 MATING AND F_2 SURVIVABILITY DATA

Group Number	I	II	III	IV	V
Dosage Group	Ethanol Control	Saline Control	PNP, 50 mg/kg	PNP, 100 mg/kg	PNP, 250 mg/kg
No. of Matings (F_1)	21	22	17	18	24
No. of Pregnancies	16	11	15	12	14
Fertility Index	76%	50%	88%	67%	58%
No. Litters Born	16	11	15	12	14
Gestation Index	100%	100%	100%	100%	100%
No. of Pups Born (F_1)	155	111	115	157	125
No. of Pups Born Alive	151	107	115	156	124
No. of Pups Alive Day 4	148	79	115	150	118
Viability Index	97%	96%	100%	99%	99%
No. of Pups Weaned	148	78	115	150	117
Lactation Index	100%	99%	100%	100%	99%
Mean Litter Size Born:	9.4	9.7	7.7	13.0	8.9
No. Male Pups	4.9	4.0	3.7	6.9	4.8
No. Female Pups	4.2	5.7	4.0	6.1	4.1
Mean Weight of Pups at 24 hrs:					
Males (g)	6.6	6.5	6.9	6.1	6.6
Females (g)	6.1	6.1	6.1	5.8	6.1
Mean Weight of Pups at Weaning:					
Males (g)	41.2	48.3	43.7	37.4	41.7
Females (g)	40.0	44.7	40.2	36.8	39.5

APPENDIX R

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance Office certifies the following:

a. This study was conducted in accordance with:

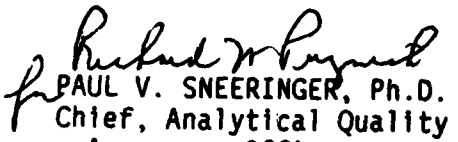
(1) Standing Operating Procedures developed by the Toxicology Division, USAEHA.

(2) Proposed Guidelines for Registering Pesticides in the United States; Hazard Evaluation: Humans and Domestic Animals, 43 FR 37384-37388, 22 August 1978.

(3) Proposed Rules, Health Effects Test Standards for Toxic Substances Control Act Test Rules and Proposed Good Laboratory Practice Standards for Health Effects, 44 FR 44089-44092, 26 July 1979.

b. Facilities were inspected during its operational phase to ensure compliance with paragraph a, above, for this study.

c. The information presented in this report accurately reflects the raw data generated during the course of conducting this study.



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